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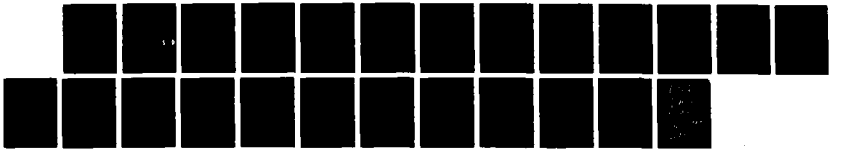

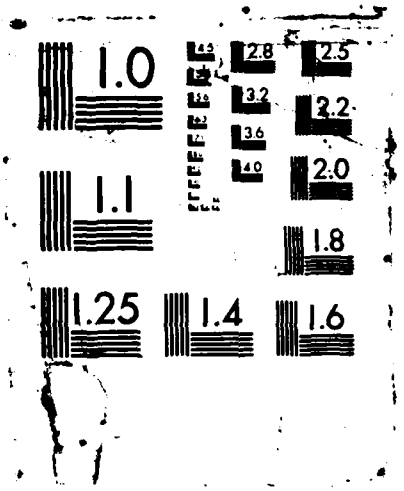
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Modulation of Human Plasma Fibronectin Levels Following Exercise

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Abstract

Elevated reticuloendothelial function and plasma fibronectin (PF) level correlate with reduced rat heat shock mortality. Thus, procedures that enhance human PF level may improve survival after such environmental stress. Both short (STE: N=14) and two identical long (LTE-1, N=14; LTE-2, N=19) term exercise programs were evaluated for their ability to increase male human PF. STE (1 week) consisted of treadmill running (0% grade) in a hot environment (41° C, 39% relative humidity). LTE (12 weeks) consisted of running and/or weight training. Both STE and LTE-2 had a significantly ($p<0.05$) higher mean initial PF level than LTE-1. STE (337.1 ± 22.8 vs. 372.5 ± 17.0 $\mu g.ml^{-1}$), LTE-1 (266.0 ± 13.0 vs. 348.0 ± 18.8 $\mu g.ml^{-1}$), and LTE-2 (370.9 ± 13.8 vs. 413.6 ± 12.5 $\mu g.ml^{-1}$) all resulted in significant ($p<0.05$) increases in PF, after program completion. Therefore, with diverse exercise training programs PF elevations were realized, even when initial concentration was high or the program was of short or long duration. However, PF level was suppressed in LTE-2 for 8 weeks before elevations occurred at 12 weeks. Thus, STE may be a more appropriate approach to the elevation of PF with exercise.

Indexing Terms: Environmental stress, reticuloendothelial function, shock

Introduction

Tissue and plasma fibronectin (PF) represent two forms of this large molecular weight (440 kilodaltons) glycoprotein (17). While the tissue type is cell-associated and important to cell adhesion and shape, PF circulates in the blood and serves as a nonspecific opsonin for the reticuloendothelial system (RES). Although it may not participate in all forms of RES clearance (23), PF is an important contributor to this RES function (1,19,21,22). It supports particulate clearance by binding to material released to the vascular space as the result of tissue injury and thereby enhances the engulfment of this debris by the phagocytic cells of the RES (22). In this way, PF influences blood vessel patency and continued blood flow. Augmentation of particulate clearance by PF is perhaps one explanation for the correlation between elevated RES function and increased survival after shock.

RES function and PF are suppressed after shock and trauma (12,16,22,25,26). Trauma-induced organ failure correlates with reduced PF level (22,24,25). While PF concentration rapidly recovers in survivors that have experienced traumatic episodes, it remains suppressed in nonsurvivors (22,25). Immunoglobulin reduction of PF results in decreased phagocytosis and decreased resistance to shock (13). Moreover, experimental rat heat stress mortality rate is significantly lessened by increased RES clearance capacity (10) and naturally occurring elevations in PF level (9). Hence, elevation of PF may influence the outcome of trauma and correlate with the degree of tolerance to environmental stress. This study was undertaken to evaluate the potential of exercise as a means of increasing circulating PF concentration in human subjects.

Materials and Methods

Exercise Programs:

For convenience, the programs studied were categorized as short (STE) and long (LTE) term exercise. The distinction as STE reflected the fact that this protocol was completed after only one week, whereas in LTE, subjects were trained for a 12 week period.

STE subjects (N=14) were human males with a mean age and weight of 28.4±1.9 yr and 79.8±3.8 kg, respectively. These subjects participated in a self-paced heat acclimation protocol. Subjects ran on a treadmill (0% grade) at an environmental temperature of 41° C and a relative humidity of 39%. They were exposed to these environmental conditions for a total of 100 min each day for 7 days, which was divided into a series of run-rest cycles. Run cycles were for 5 (N=6), 8 (N=2), and 10 (N=1) min, while rest cycles were for 2 (N=2), 5 (N=6), and 10 (N=1) min. Total run and rest times were 56 and 44 min, respectively. Work load was selected by each individual and involved between 63 to 72% of their maximum oxygen consumption ($VO_{2\,max}$). Samples for PF testing were collected just prior to the start of the program and 24 h after program completion.

Two identical LTE programs were evaluated (LTE-1, N=10 and LTE-2, N=19). Subjects were human males with a mean age and weight of 23.7±3.8 yrs and 75.4±9.0 kg, respectively. The exercise procedures employed were those previously described in a study to compare the effects of physical training on fitness test scores and load bearing performance (15). Volunteers were randomly placed in one of the following training groups. Group A

performed heavy resistance weight training for both the upper and lower body musculature 4 days a week, which was conducted on Monday (M), Tuesday (T), Thursday (Th), and Friday (F). In addition, 4 days a week (M,T,Th, and F), high intensity endurance run training was conducted. This running exercise was of two types, carried out on alternate days of exercise. Type 1 was distance running for 40 min in which subjects exercised at 70 to 80% of their $VO_{2\,max}$. Type 2 was interval running (20% of total mileage.week^{-1} obtained in the type 1 run), which was performed at 90-100% of their $VO_{2\,max}$. Subjects in group B conducted heavy resistance weight training for only the upper body musculature 4 days a week (M,T,Th, and F) and performed high intensity endurance run training, as previously described. Heavy resistance weight training for both the upper and lower body was performed 4 days a week (M,T,Th, and F) by group C. Group D conducted only high intensity endurance run training 4 days a week (M,T,Th, and F). Training times for groups A,B,C, and D were approximately 180, 160, 120, and 90 min.day^{-1} of exercise, respectively, which were performed over a 12 week period. In the LTE-1 study, initial and ending PF samples were collected, while in LTE-2 additional samples were collected at 4 week intervals over the 12 week program. All samples were obtained prior to the performance of any exercise, to ensure that the measurements represented the PF resting response to training.

Plasma Fibronectin Quantification:

PF level was determined immediately after sample collection using the turbidimetric assay procedure (2,9,20). Commercial kits to perform this assay were obtained from Boehringer Mannheim Biochemicals (Indianapolis, IN). Blood was collected in ethylenediaminetetraacetate-anticoagulant tubes that

contained an inhibitor for proteolytic enzymes (Aprotinin; Sigma Chemical Co., St. Louis, MO). Samples were centrifuged (1000xg) under refrigeration to obtain the plasma. Ten μl of plasma were added to 1 ml of the PF-antiserum buffer and mixed. At 1 min, the sample absorbance was read in a spectrophotometer at a wave length of 365 nm. A second absorbance reading was made at 10 min. The 1 min value was subtracted from the 10 min value to obtain the change in absorbance for the sample. The change in absorbance determination was then compared to a standard curve for change in absorbance for known concentrations of human PF. PF values were reported as μg of PF.ml^{-1} of plasma. Sample PF concentration was determined in triplicate.

Statistical Analysis

The paired t test was used to determine significant differences between PF levels before and after exercise. Analysis of variance with or without repeated measures followed by Tukey computation (28) were employed to determine significant differences in PF levels and percent of initial PF level among and within the exercise studies. Chi square was employed for frequency data analysis. For all statistical tests, level of significance was chosen as $p<0.05$. Except where noted, reported PF values are means $\pm$S.E.

Results

For all human subjects (N=43), the mean initial PF level was 335.5$\pm$10.9 μg.ml^{-1}. Normal circulating levels of this protein ranged between 221 and 525.7 μg.ml^{-1} of plasma.

Figure 1 illustrates the changes in PF after the STE and LTE programs. Comparing levels before and after exercise revealed that regardless of the exercise program employed, mean PF was significantly elevated after program completion. As shown in table 1, mean initial PF level for subjects in LTE-1 was significantly less than that of subjects in the STE or LTE-2 studies. After exercise, more subjects in LTE-1 had increased PF values than did subjects in LTE-2 or STE, but this increase was not significant. However, LTE-1 did have a significantly greater increase in the mean percent of the initial PF level after exercise. For LTE-2 and STE, mean initial PF level for those individuals who did not experience an increase in PF after exercise was not significantly greater than those who did have an elevation.

LTE-2 was associated with reductions in PF before an elevation in level occurred (Fig. 2a). Reductions were found over the first 8 weeks. This was true for all exercise regimens employed (Fig. 2b). No significant differences were noted in the initial PF levels among the four groups (Table 2). Analysis of the separate exercise regimens revealed that group C had a significantly decreased PF value at week 4 and experienced the lowest number of subjects with increases in PF after program completion. Only groups A and B demonstrated a significant increase in PF level after 12 weeks. However, analysis of the combined groups showed that PF was significantly decreased at 4 and 8 weeks and significantly increased after 12 weeks.

Discussion

This study determined the effect of various exercise training programs on human PF concentration. This glycoprotein is important to RES clearance function and early recovery of human PF level after trauma is generally

correlated with a positive outcome (22,25). Moreover, naturally occurring elevated PF concentrations prior to heat stress are associated with increased rat survival (9). Although human PF is abnormally increased under conditions of pathology, such as in obesity (6), cancer (3), proteinuria (4), diabetic retinopathy (5), and preeclampsia (27), in the absence of disease, PF elevations perhaps signal enhanced RES function and resistance to trauma. Therefore, in healthy individuals, PF augmentative procedures may improve survival after traumatic episodes such as heat stress.

Zerlauth and Wolf noted that with different assay methods the range for normal human PF can be large (29). As determined from the findings reported here, normal circulating levels were also within a broad range. Moreover, groups of human subjects could have significantly different initial mean PF values. This did not seem to be the result of seasonal variability, since some exercise studies with significantly different initial PF levels (STE and LTE-1) were evaluated in the same month, but one year apart. An explanation for this variability is not known, but may relate to possible differences in the reactive nature of the PF test kit elements (2). Though test kit lots were the same within a study, because of the time span between studies, the same lot could not be used.

In spite of this initial PF level variability, completion of diverse forms of exercise training was associated with significant elevations in this glycoprotein (Fig. 1). Initial PF concentration did not appear to affect the outcome, for in the two LTE studies, even when initial level was significantly elevated (LTE-2, Table 1), a further increase in PF was found after training (Fig. 1). Furthermore, although LTE-1 subjects had a significantly lower mean initial PF level, the percent of individuals with PF elevations after program completion

was not significantly greater than that noted for LTE-2 (Table 1). Finally, mean initial PF concentration for individuals that did not experience an increase in PF after program completion was not significantly greater than the value determined for subjects in which training was associated with PF elevations (LTE-2 and STE; Table 1). These findings suggested that initial level did not appear to be a critical factor determining whether or not there was an increase in PF after training. This was best illustrated by one subject in the LTE-2 study (group D) who had an initial PF value (525.7 $\mu g.ml^{-1}$) that was significantly greater than the mean value determined for all subjects (335.5 ± 71.3 $\mu g.ml^{-1}$; mean $\pm$ standard deviation). Even with such a high starting concentration, this individual experienced an increase in PF (584.4 $\mu g.ml^{-1}$) after completion of the exercise training program.

Although PF could be increased even when initial level was high, starting concentration did influence the degree of PF augmentation with exercise. This conclusion was supported by the finding that when initial PF concentration was significantly less, a significantly greater increase in the percent of the initial PF level was obtained after exercise (LTE-1 vs. LTE-2, Table 1). Therefore, the lower the initial level the greater the degree of influence the exercise training program had on PF elevation.

The STE and LTE programs were composed of many factors that could affect the stress level to which an individual was subjected. STE was self-paced, intermittent, occurred for a relatively short time period (100 $min.day^{-1}$; 1 week) at an elevated environmental temperature, and did not exceed a $VO_{2\,max}$ of 72%. In contrast, both LTE studies occurred for a longer time period (180 to 90 $min.day^{-1}$ of exercise; 12 weeks) and subjects that performed high intensity endurance run training were estimated to obtain at

least a 90% $VO_{2\,max}$. This suggested that the LTE program was more stressful than STE. LTE-2 and STE studies had no significant differences in their initial PF levels, percent of subjects with increased PF, and mean percent of initial PF level after program completion (Table 1). In addition, both were associated with a significant increase in PF (Fig. 1). Therefore, although the training intensity for STE may not have been as great, this reduced stress level did not significantly alter the outcome. Unfortunately, the STE study design did not distinguish the separate contributions made by exercise and exposure to elevated environmental temperature. Because it was of short duration (1 week) and involved less intense exercise ($VO_{2\,max} \leq 72\%$), exposure to a hot environment may have played an essential role in the PF elevations.

Different forms of stress such as surgery (20), traumatic shock (22), and burn injury (16) induce tissue damage and reduce PF level. This reduction may be the result of rapid PF binding at sites of injury, which perhaps represents the beginning of the wound-healing process (7,8,18). The curves illustrated in figure 2 were typical for the PF response to stress, for they demonstrated first suppression, recovery, and then an elevation (16,26). Though LTE-2 was composed of different exercise regimens, the evaluation of the PF response could be studied as one (Fig. 2a), since all regimens were associated with a similar PF response (Fig. 2b). LTE-2 appeared to be of sufficient stress to significantly reduce PF values over the first 8 weeks of the program (Fig. 2, Table 2). Because of the small subject number (≤ 5) per group, the presence of significant changes in PF level was only readily apparent when the groups were combined (N=19, Table 2). Even with a small subject number, groups A, B, and C did have significant changes in PF level. Thus, the combination of significant PF suppression at 4 weeks and a low percent of subjects with PF elevations at 12 weeks suggested that weight

training in the absence of running (group C; Table 2) was the least advantageous type of exercise for the augmentation of this glycoprotein. Moreover, since only running in combination with weight training was associated with significant increases in PF (groups A and B; Table 2), a synergistic effect between these forms of exercise was indicated. The separate and combined effects of running and weight training are not easily explained, but likely exert their influence on fibronectin synthesis (14) and exchangeable sites (7,8) within the body. Comprehension of the exercise effects on these PF restorative mechanisms is necessary before a fuller insight on PF modulation with exercise can be obtained.

As demonstrated by this study, elevations in human PF occurred after various exercise training programs. However, with the most stressful protocol (LTE-2), PF was suppressed in the course of training before an increase was noted. Since comparable increases were observed for both STE and LTE, if the purpose were solely to raise PF level, then a less stressful exercise program (STE) might be more appropriate. Because RES function is important to survival after shock or trauma (9,10,12,22,25,26), PF suppression with stressful exercise suggests an enhanced risk for lethal shock during the phase of this suppression. Fatal human heat shock can occur in the early phase (day 2) of a high intensity exercise program (11). Suppression of this mediator of RES clearance may correlate with human heat fatalities induced by such programs. Hypothetically, monitoring PF before and during the initial phase of a training program may help to identify those individuals most susceptible to exercise-related PF suppression and potentially guard against such fatalities. The results of this investigation, as well as others (9,22,25) suggest that this hypothesis deserves further study.

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Table 1. Differences in mean initial plasma fibronectin Level[#] (MIPFL; $\mu g.ml^{-1}$), percent (%) of subjects with increased plasma fibronectin level (PFL), mean percent of initial PFL[#] and mean PFL ($\mu g.ml^{-1}$) after exercise for short term exercise (STE) and two identical long term exercise (LTE-1 and LTE-2) studies.

	MIPFL for all Subjects	% Subjects with Increased PFL after Exercise	Mean % of Initial PFL after Exercise	MIPFL for Subjects Without Exercise-Induced PFL Elevation	MIPFL for Subjects With Exercise-Induced PFL Elevation	Mean PFL for all Subjects after Exercise
STE	337.1 ±22.8	64.3	113.2 ±5.3	366.8 ±31.7	320.5 ±22.0	372.5[Q] ±17.0
LTE-1	266.0[*] ±13.0	100.0	128.9[λ] ±5.5		266.0 ±13.0	348.0[Q] ±18.8
LTE-2	370.9 ±13.8	78.9	112.7 ±2.9	404.0 ±21.0	362.0 ±16.0	413.6[Q] ±12.5

values are means ± standard error
* value is significantly ($p<0.05$) less than either the STE or LTE-2 value
λ value is significantly ($p<0.05$) greater that either the STE or LTE-2 value
Q value is significantly ($p<0.05$) greater than the MIPFL for all subjects

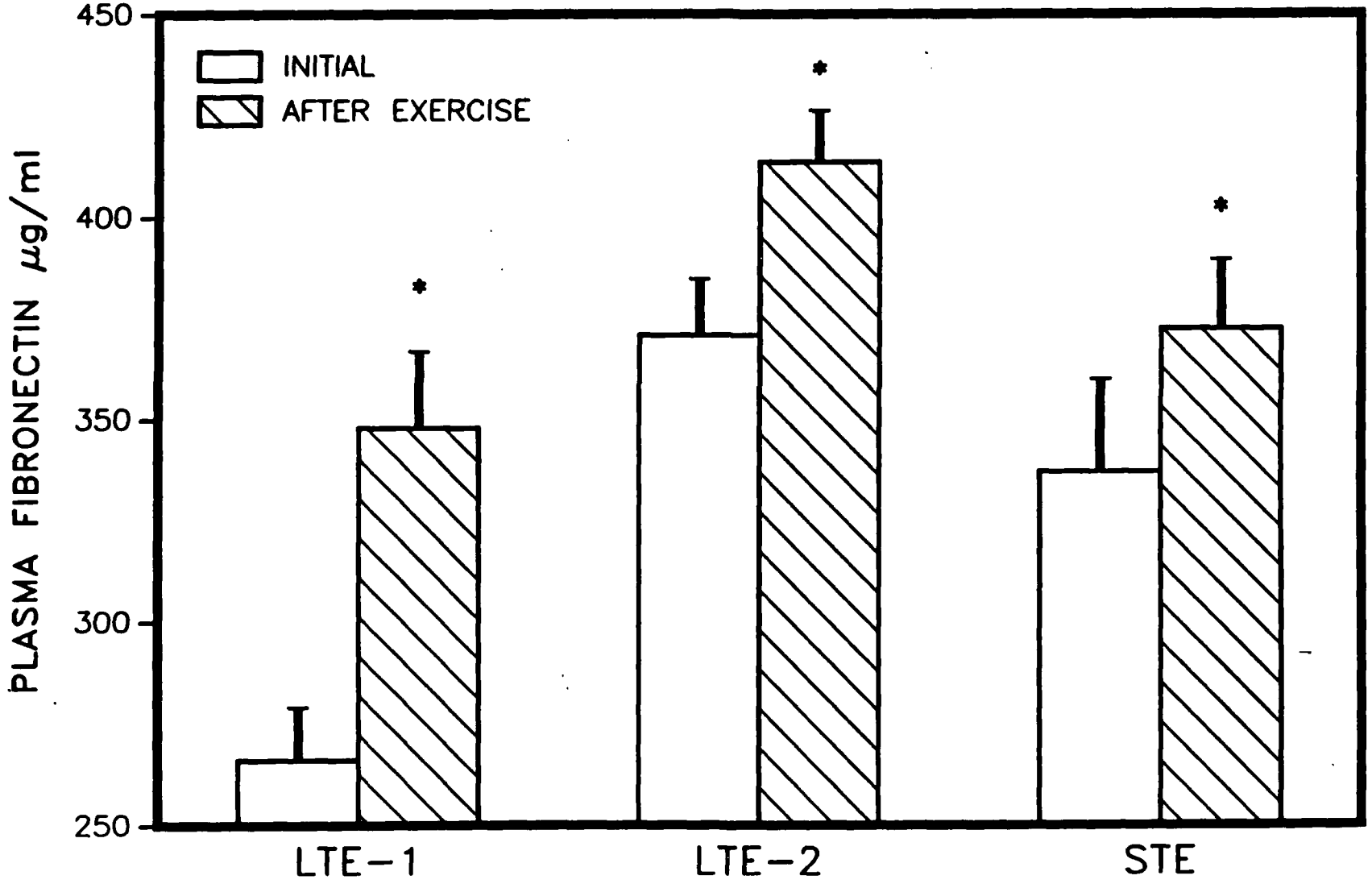
Table 2. Comparison of mean plasma fibronectin level (PFL)[¥] and percent with increased PFL in the course of long term exercise study #2.

Group	Mean PFL ($\mu g.ml^{-1}$)				% with increased PFL after exercise
	Initial	Weeks of Exercise 4	8	12	
A (N=5)	358.9 ±32.7	317.9 ±16.9	329.3 ±25.4	404.5* ±17.2	80.0
B (N=5)	341.3 ±19.3	316.3 ±14.3	331.6 ±17.5	400.4* ±13.1	100.0
C (N=5)	375.9 ±7.8	302.0* ±19.7	335.9 ±15.4	405.1 ±22.4	40.0
D (N=4)	416.5 ±42.0	364.8 ±32.9	380.7 ±52.5	453.6 ±46.5	100.0
All Groups (N=19)	370.9 ±13.8	323.2* ±10.8	339.6* ±15.0	413.6* ±12.5	78.9

¥ values are means ± standard error
* significantly ($p<0.05$) different from the initial value

Figure 1. Comparison of plasma fibronectin levels after short term exercise (STE) or two identical long term exercise (LTE-1 and LTE-2) studies.

* significantly ($p<0.05$) different from the initial value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LTE−1
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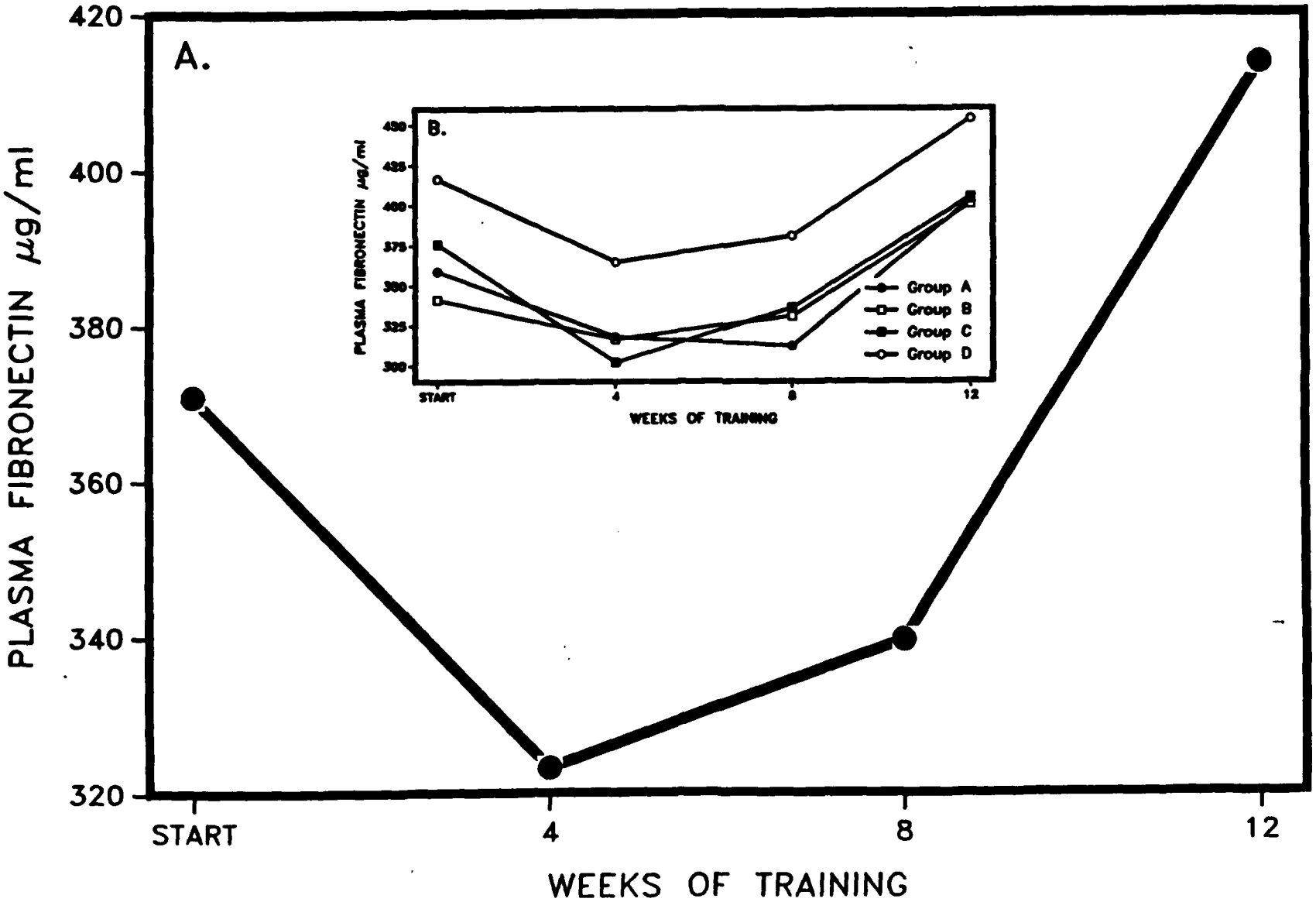
Figure 2. Combined effects of the various exercise regimens within long term exercise study #2 on plasma fibronectin level (A). Separate effects of the various exercise regimens (groups A,B,C, and D) within long term exercise study #2 on plasma fibronectin level (B).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Group C
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DISCLAIMER

The investigators adhered to the "Guide for Laboratory Animal Facilities and Care as promulgated by the committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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